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PALI-2108, a New GI-Activated PDE4 Inhibitor Promotes Clinical Response in UC Patients Within One Week of Treatment

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INTRODUCTION AND AIM

Systemic phosphodiesterase-4 (PDE4) inhibitors are used as a treatment strategy for inflammatory diseases; however, current therapies are constrained by adverse effects (AEs) linked to peak systemic exposure (C_{max}). PALI-2108 is a microbiome-activated oral, once-daily prodrug designed to enable PDE4 inhibition within the GI tract. We evaluated the pharmacokinetic (PK) and pharmacodynamic (PD) profile of PALI-2108 alongside early clinical activity in ulcerative colitis (UC).

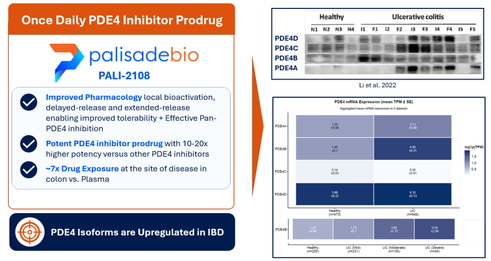


Figure 1: Localized bioactivation of PALI-2108 prodrug results in improved PK characteristics including delayed-release and extended-release of active PDE4 inhibitor targeting the diseased tissues of the colon overexpressing PDE4 A,B,C, and D (Western Blot above and mRNA Expression) and improving GI and CNS tolerability versus immediate release and non-localized PDE4 inhibitors

METHODS

Safety, tolerability and PK were assessed in NHVs receiving ascending single (n=40) and multiple (n=32) oral doses of PALI-2108, including a food-effect (FE) cohort 150 mg crossover (fed vs fasted; n=12). UC patients [n=5, modified Mayo (mMayo 5-9; endoscopic subscore ≥2)] received PALI-2108 30 mg BID for 7d, including a 5d dose titration. mMayo score, histologic indices (Nancy, Robarts, Geboes), colonic tissue lymphocyte density, fecal calprotectin (FCal), plasma hsCRP, and tissue PDE4B expression were evaluated at baseline and at 7d. Exploratory analyses evaluated PK/PD relationships and inflammatory signaling markers including cyclic adenosine monophosphate (cAMP) levels. We performed PathAI quantitative digital pathology to evaluate immune cell contribution in both tissue (lamina propria (LP) and mucosal) and plasma along with structural changes in mucosa (hematoxylin and eosin).

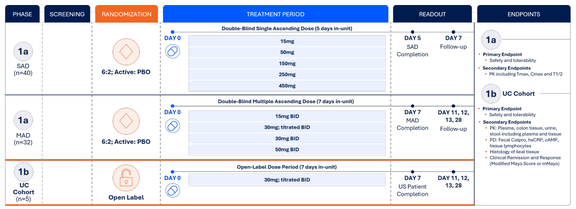


Figure 2: Phase 1a/b study of PALI-2108 in NHV and an open-label study of UC patients (NCT06663605).

RESULTS

Phase 1a SAD/MAD Cohorts Demonstrate Favorable PK and Superior Exposure Compared with Other PDE4 Inhibitors

Dose Proportionality and Extended Half-Life Enabling Daily Dosing

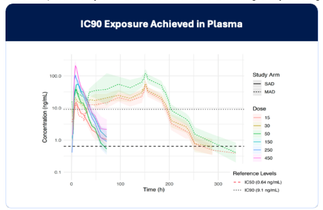


Figure 3: PK profile of the Phase 1a SAD/MAD cohort

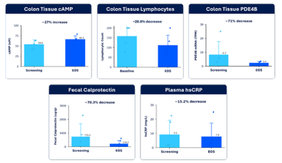
Single Ascending Dose (SAD)
PALI-2108 (prodrug; data not shown)
- T_{max}: ~3-4hr → consistent with small intestinal dissolution (Eudragit + prodrug design)
- **Exposure (AUC):** Minimal, as intended (GI-restricted)

PALI-0008 (active PDE4 inhibitor)
- T_{max}: ~8-9hr → consistent with ileocolonic bioconversion
- **PK profile:** Extended release/ ~2-3x longer half-life than other PDE4 inhibitors (usually BID)
- **Dose proportionality:** C_{max} and AUC approximately dose-proportional

Multiple Ascending Dose (MAD)
Bioconversion
- PALI-2108 converted locally to PALI-0008 in terminal ileum/colon
- **Steady State**
- Reached within ~48 hrs
- Stable pre-dose troughs with repeat dosing
- Pre-dose troughs ~20% higher than single-dose C_{max}, above IC90
- **Dosing Implications**
- Extended half-life supports **once-daily dosing**

PALI-2108 Demonstrates Consistent PD and Biomarker Improvements in UC Patients

Figure 4: (top row) PALI-2108 increased cAMP in 4/5 patients; colon tissue lymphocytes decreased in 4/4 patients; and tissue PDE4B expression decreased in 5/5 patients. **(bottom row)** Fecal calprotectin decreased in 4/5 patients and plasma hsCRP decreased.



+27% **Tissue cAMP was increased** in 4/5 patients as expected

-29% **Tissue lymphocytes were decreased** in 4/4 patients

-71% **Tissue PDE4B was decreased** in 5/5 patients

-70% **Fecal calprotectin was decreased** in 4/5 patients

-15% **hsCRP was decreased** by a mean of 15.2%

PALI-2108 Improves Histological Outcomes, Clinical Response, and Remission in UC Patients

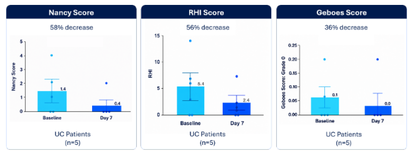
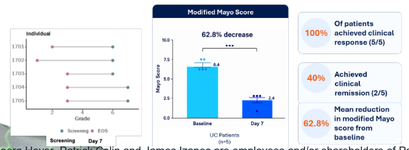


Figure 5: (upper panel) PALI-2108 shows reductions in Nancy score, RHI, and Geboes score. **(lower panel)** mMayo score significantly decreased (***P<0.001) with PALI-2108.



100% Of patients achieved clinical response (5/5)

40% Achieved clinical remission (2/5)

62.8% Mean reduction in modified Mayo score from baseline

PALI-2108 Reduces Tissue Inflammatory Cell Counts in UC Patients

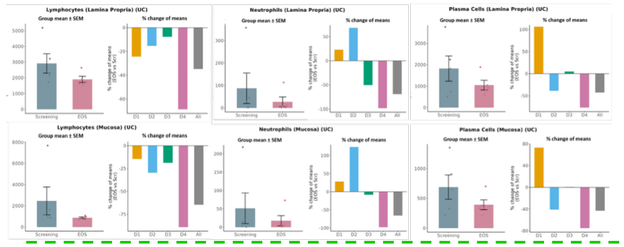


Figure 6. PathAI-enabled quantitative digital pathology analysis demonstrated reductions in inflammatory cell counts in LP and mucosal tissue in individual patients (n=5) over 1 week.

PALI-2108 Induces Early Histologic Features of Mucosal Healing in UC Patients

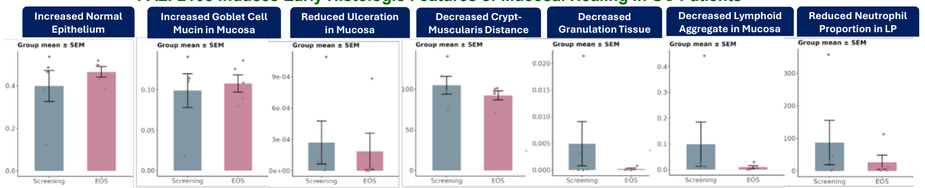


Figure 7. Representative histopathology showing PALI-2108–induced structural changes consistent with mucosal healing, including increased normal epithelium, goblet cells, and mucin, and reduced ulceration, crypt-to-muscularis mucosae distance, granulation tissue, lymphoid aggregates, and LP neutrophils.

Proposed Phase 2 Study Design in UC (Study Initiated)

Figure 8. Phase 2 randomized, blinded long-term extension (remission maintenance) in UC patients.

SUMMARY

PALI-2108 demonstrated PK consistent with targeted ileocolonic delivery and once-daily dosing, with 30 mg QD maintaining PALI-0008 exposure above IC90 for 24 hours.

PALI-2108 was well tolerated and demonstrated target engagement and early activity in UC, including ↓PDE4B, ↑cAMP, reduced inflammation, improved histology, 100% clinical response, and early remission.

Early histologic features of mucosal healing were observed, including reductions in inflammatory cells in plasma and tissue.

These findings support continued development of PALI-2108 as a differentiated, ileum- and colon-targeted oral PDE4 inhibitor prodrug for IBD.

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